



Motoo Kimura
(1924–1994)

FOR decades the field of mathematical population genetics and evolutionary theory was dominated by the three pioneers, J. B. S. HALDANE, R. A. FISHER, and SEWALL WRIGHT. With WRIGHT's death (CROW 1988), and for some time before, the leading successor to this great heritage was MOTOO KIMURA. Although best known for his daring neutral theory of molecular evolution, a concept of great interest and equally great controversy, he is admired by population geneticists even more for his deep contributions to the mathematical theory.

MOTOO KIMURA was born November 13, 1924 in Okazaki, Japan. He died November 13, 1994, on the seventieth anniversary of his birth. For some time he had been a victim of amyotrophic lateral sclerosis and was progressively weakening. Nevertheless, his death was accidental. He fell, hitting his head, and never regained consciousness. Death can be merciful; he had nothing to look forward to but further deterioration.

KIMURA's father was a businessman who loved flowers and raised ornamentals in the home. Young MOTOO was fascinated by their beauty and curious as to their development. When his father bought him a microscope, he spent hours with it. In school he developed an interest in plants and decided to become a systematic botanist. At the same time he enjoyed mathematics, especially EUCLID. He showed definite promise, for his teacher advised him to become a mathematician, which advice he ignored.

KIMURA never lost his love of plants and retained an interest in botany throughout his life. He later became an avid orchid breeder, and several of his creations were

prize-winners. When our textbook (CROW and KIMURA 1970) was published, he used his royalties to build a tiny greenhouse attached to his home. Every Sunday was orchid day. He used his artistic talent to paint pictures of his favorite flowers, usually on chinaware.

From age 17 to 19 KIMURA was in high school, where a friendly and scientifically literate teacher encouraged his study of chromosome morphology, and he became a plant cytogeneticist. At that time, cytogenetics was very popular in Japan, and he joined the army of chromosome watchers. During this period he was also fascinated by a physics course. HIDEKI YUKAWA, later to win the Nobel Prize for predicting the meson, became his scientific hero, and KIMURA began to take an interest in mathematics as the language of science.

Japan was then in the midst of World War II, and the normal high school period was shortened from three to two and a half years. In 1944 he was admitted to Kyoto Imperial University. HITOSHI KIHARA was Japan's foremost geneticist (CROW 1994), a world leader in the cytogenetics of wheat, and KIMURA might have been expected to study with him. Nevertheless, KIHARA advised him to enroll in botany. There was a reason. At that time students in botany were exempt from military service until graduation. Curiously, students of agriculture—KIHARA's area—did not enjoy this privilege.

In this way KIMURA escaped military service, but life was far from easy. There was the irritation of regular military drill, and there was never enough good food. The bomb on Hiroshima came before his first university year was finished, but conditions immediately after the war were even worse. Food was even harder to obtain

and KIMURA made regular Sunday visits to a cousin for a good meal. The cousin was a quantum physicist, so these Sundays were also occasions for scientific talk.

Although still a student of cytology, KIMURA became increasingly interested in mathematical questions. He was first attracted to mapping functions and through this learned of J. B. S. HALDANE. Reading DOBZHANSKY's *Genetics and the Origin of Species* led him to the work of SEWALL WRIGHT. By this time, the war was over and he had moved to KIHARA's department. KIHARA was doing backcrosses in wheat to introduce parts of a genome into a different cytoplasm, and KIMURA helped him by deriving the frequency distribution of introduced chromosomes in successive backcrossed generations. This led to his first published scientific paper (KIMURA 1950).

KIHARA assigned no specific duties, and KIMURA busied himself reading WRIGHT's papers. There was only a single copy and of course no duplicating facilities, so he copied the papers by hand. (I recall, years later, seeing and marveling at KIMURA's neatly copied version of WRIGHT's 63-page 1931 paper, complete with occasional notes and derivations of his own.)

In 1949 KIMURA joined the research staff of the National Institute of Genetics in Mishima, a position he retained for the rest of his life. The laboratory was a crude wooden building that had been an airplane factory during the war. Mishima was small and provincial, a striking contrast to the intellectual and cultural attractions of Kyoto, but on clear days it did provide a magnificent view of Mount Fuji. Actually, KIMURA spent much of his time in KIHARA's laboratory in Kyoto where there was a much better library. Studying probability textbooks, he discovered that the FOKKER-PLANCK equation that WRIGHT had used was only one of two KOLMOGOROV equations, the forward one. Later, KIMURA was to be especially creative in his use of the backward equation.

By this time KIMURA was devoting his time entirely to mathematical genetics. As was his lifetime habit, he learned the subject for himself. His formal training in mathematics was quite limited; he simply learned what he had to learn to solve the problem at hand. He was helped, of course, by being exceptionally gifted. During this time he proposed the "stepping stone" migration model (KIMURA 1953). WRIGHT's island model, the standard of the time, assumed that immigrants come at random from a larger population. KIMURA introduced the more realistic model that immigrants come from a near neighbor. By adding long-range migrants, he could include the island model as a special case.

This was a lonely period for KIMURA, for none of his associates understood his work, or thought it to be of any interest. The exception was TAKU KOMAI, also in Kyoto. KOMAI had studied with T. H. MORGAN in the United States and, although he didn't understand WRIGHT's mathematics, he encouraged KIMURA to study

his papers. That KIMURA persisted in working alone in an indifferent, if not hostile, environment was characteristic. Then, as later, he was confident of his own abilities and knew what he wanted to do.

KIMURA's chance to study abroad came through DUNCAN McDONALD, who was working with the Atomic Bomb Casualty Commission in Hiroshima. McDONALD, coming from Dartmouth College, knew that the College had a fund for support of genetics and was generous with it. This, plus a Fulbright travel fellowship, allowed KIMURA to come to the United States. McDONALD thought he should study with WRIGHT, but WRIGHT was considering retirement and recommended that he go to Iowa State University with J. L. LUSH.

My acquaintance with KIMURA began as he was just starting his graduate work at Iowa State. We met by accident in the University of Wisconsin Union where the Genetics Society was meeting. I had heard of KIMURA through my student, NEWTON MORTON, who had been McDONALD's colleague in Hiroshima. I must have been almost unique in the United States in recognizing the name KIMURA. Thus began a friendship that lasted for the rest of his life. He brought with him a paper that he had written on the ship between Japan and Seattle. The paper dealt with fluctuating selection coefficients. I was greatly impressed, for he had found a transformation that converted a cumbersome partial differential equation into the familiar expression for heat conduction. The paper was reviewed by WRIGHT, who praised it lavishly—unusual for WRIGHT—and it was published in *GENETICS* (KIMURA 1954).

KIMURA soon became dissatisfied with the direction of research at Iowa State, with its emphasis on subdivision of epistatic variance. Finding little interest there in stochastic models, he wrote asking to work with me at the University of Wisconsin. I gladly accepted and he came to Wisconsin early in the summer of 1954. Before the summer was over, he had worked out the complete solution of neutral random drift in a finite population (KIMURA 1955). A few months later, WRIGHT moved to Madison, and KIMURA finally had his dream—a chance to study with WRIGHT. Actually, although there was mutual admiration, they never worked together. Their approaches were too different.

KIMURA was invited to the Cold Spring Harbor Symposium of 1955, where he met the leading population geneticists. The attendees by this time had heard of the Japanese phenomenon, although most could understand neither his mathematics nor his English. Another meeting at Stony Brook allowed him to meet H. J. MULLER, whom he greatly admired, and they became regular correspondents. KIMURA always insisted that MULLER should occupy a place among the great pioneers in evolutionary thinking.

His two years in Wisconsin as a graduate student were remarkably productive. He wrote a number of papers extending the drift model to multiple alleles, mutation,

migration, and selection. It was during this period that he first used the KOLMOGOROV backward diffusion equation to find the probability of ultimate fixation of a mutant with arbitrary dominance, a finding later to be of great use in molecular evolution. During this period, KIMURA worked out the conditions for a stable equilibrium in a multi-allelic locus and for the evolution of closer linkage by selection with epistasis. He also wrote a paper extending FISHER's fundamental theorem of natural selection to include dominance, epistasis, and changing environment. KIMURA was one of the early ones to interpret FISHER's theorem, a game that still goes on with no signs of abatement. This is a remarkable set of accomplishments for two years, especially considering that he was completing the genetics, language, and mathematics requirements for the Ph.D., awarded in 1956.

Returning to Japan, KIMURA continued to produce one important paper after another. His skill in manipulating the KOLMOGOROV equations and applying them to significant evolutionary problems was outstanding. He and I continued to work together. He spent some time in Madison, and I visited Japan several times. Between visits we had a trans-Pacific collaboration by correspondence.

Here are a few of KIMURA's significant findings. I have already mentioned the "stepping stone" model of population structure, which has been the starting point for investigations by many authors. He discovered the phenomenon of "quasi-linkage equilibrium," a bit ironic considering his lack of interest in subdividing epistatic variance earlier at Iowa State. He showed that with loose linkage, the population generates just enough linkage disequilibrium to cancel the epistatic variance, so that the additive variance, *without* epistatic terms, is the best predictor of change under selection. I suspect that this finding gave him a certain malicious pleasure. With H. KAYANO he analyzed a case of meiotic drive in *Lilium*, calculating the equilibrium balance between excess transmission of b chromosomes in embryo sac mother cells and the viability decrease from extra numbers. He did a number of studies of genetic load. In one study he showed that the mutation load can be reduced with epistasis, but only when there is sexual reproduction. He was also the first to consider the mutation and segregation loads in finite populations. (His first calculations, done when computers were primitive, involved some very inventive, and to some critics dubious, approximations. Later computer work has vindicated them.) He wrote two influential papers on inbreeding theory, introducing a new probability method and showing that WRIGHT's maximum avoidance of inbreeding was not the best way to preserve heterozygosity in the long run. He showed how to calculate the selective efficiency of truncation selection and its load-reducing effect. Of particular importance in practical application was the surprising result that a very crude

approximation to truncation selection is almost as effective as strict truncation. This made the theory much more realistic for natural populations.

KIMURA's early Wisconsin work on the probability of fixation of a new mutant was followed by studies of the average time until fixation, the time until loss, the number of individuals carrying the mutant gene and the number of heterozygotes during the process, the age of a neutral mutant in the population, and, more generally, the moments for the sum of an arbitrary function of allele frequency during the process. A curious result was his showing, with T. MARUYAMA, that the time required for fixation of a selectively favored mutation is the same as for a deleterious one, despite the enormous differences in the probability of occurrence. Finally, KIMURA was associated with the origin of three classical models of mutation, widely used in population genetics, the "infinite allele," the "infinite site," and the "ladder" models. I was associated with some of the work mentioned in these two paragraphs, a source of deep satisfaction to me, for I could never have done the mathematics alone.

I shall not list KIMURA's papers individually. A selection of his best papers was published recently (KIMURA 1994). The book was edited by NAOYUKI TAKAHATA, who also provided introductory comments to the various papers, putting them in context and showing how they have influenced subsequent work. I won't try to summarize this great volume of work, but I will list the sections of the book to give some idea of KIMURA's versatility. The section headings, with the number of papers in parentheses, are as follows:

1. Random gene frequency drift (4)
2. Fluctuation in selection intensity (2)
3. Population structure (3)
4. Linkage and recombination (4)
5. Evolutionary advantages of sexual reproduction (1)
6. Natural selection (2)
7. Meiotic drive (1)
8. Genetic load (3)
9. Inbreeding systems (2)
10. Evolution of quantitative characters (4)
11. Probability and time of fixation or extinction (5)
12. Age of alleles and reversibility (4)
13. Intergroup selection (1)
14. Infinite allele, infinite site, and ladder models (3)
15. Molecular evolution (2)
16. Nucleotide substitutions (3)
17. Molecular clock (3)
18. Neutral theory (10)

The book includes a bibliography of KIMURA's major publications, a total of 161. Altogether, he wrote about 660 papers and 6 books. Although he had several collaborators, most of these publications are his alone.

KIMURA's blockbuster was his neutral theory, first presented in 1968 (and independently by KING and JUKES

1969). He was first led to this heretical view by the realization that, if all nucleotides in the genome evolved at the rates recently found in the few proteins that had been studied, this would require an enormous amount of selection, more than seemed possible. He therefore argued that the great bulk of DNA changes must be neutral, with evolutionary dynamics determined by mutation and random drift. Fortunately, many of his earlier mathematical studies turned out to be preadapted to the study of molecular evolution, for example, the probability of and time until fixation of a new mutant. He spent most of the remainder of his life elaborating this theory and defending it. He wrote a highly influential book (KIMURA 1983), on which he spent a great deal of effort. At first the theory was laughed out of court by most students of evolution, but it gradually gained adherents.

Promoting and defending the theory became an obsession with him, and he lost no opportunity to argue for its importance. Discussion was not a matter of give and take, but of polemics. He was inventive in continuously finding new evidence, as new facts emerged. Although he never denied the role of natural selection in the evolution of form and function, he emphasized it less and less. Actually, his theory needed no such impassioned advocacy. It could stand on its own.

The neutral theory, *qua* theory, has been highly successful. For heuristic value, it must be counted as one of the great ideas of contemporary evolution, for it has generated a whole research industry. That a great deal of nucleotide substitution and polymorphism is by random drift is, I think, no longer in doubt. The relative importance of random drift and selection in determining rates of protein evolution is less clear. The detailed resolution of molecular and organismic evolution is still incomplete. But at a minimum, KIMURA has brought out most emphatically the fact that any adequate treatment of molecular evolution must be stochastic.

KIMURA received almost all of the honors and prizes for which an evolutionary biologist is eligible. These include the following: Genetics Society of Japan Prize, 1959; Weldon Memorial Prize, Oxford, 1965; Japan Academy Prize, 1968; Japan Society of Human Genetics Prize, 1970; Foreign Member, National Academy of Sciences USA, 1973; Japanese Order of Culture (Emperor's medal), 1976; Chevalier de L'Ordre National du Mérite, 1986; Asahi Shimbun Prize, 1987; John J. Carty Award, National Academy of Sciences, USA, 1987; Genetical Society of Great Britain, honorary member, 1987, and International Prize for Biology, 1988; The Darwin Medal, Royal Society, 1992; Foreign member of the Royal Society, 1993. He has received honorary degrees from the Universities of Chicago and Wisconsin.

What is KIMURA's place in the history of genetics and evolution? There are two important leaders after the great trio. One is the mathematician, GUSTAV MALÉCOT,

whose work, published in obscure French journals, was for a long time neglected by English speakers. The other, of course, is KIMURA. Both were theorists. But while MALÉCOT was a mathematician's theorist, KIMURA was a biologist's theorist. MALÉCOT was interested in elegance, rigor, and completeness (NAGYLAKI 1989). KIMURA always had a biological problem in mind and pursued one biologically significant question after another. He solved problems, but he also formulated them.

KIMURA is best known for his neutral theory. Yet, influential as this is and despite the great impact it has had on molecular evolution, many population geneticists probably remain even more impressed by the steady flow of papers in mathematical population genetics, with their inventive solutions to important and difficult problems. He left a nearly completed paper at the time of his death (KIMURA 1995). It is not one of his great ones, but it is vintage KIMURA. He shows that the number of favorable mutations that can be simultaneously in transit toward fixation, $n < (N/2) \ln(1 - L)$, where N is the effective population number and L is the amount of excess reproduction available for selection of these mutants. If L has the reasonable value of 10%, n is less than $1/20$ the population number. This then places a limit on the rate of favorable evolution in a finite population. Like HALDANE's (1957) cost of natural selection, this value is independent of selection intensity. But KIMURA's formulation is more realistic in taking population number into account and not depending on the initial frequency of the mutation. He hadn't lost his touch.

What about KIMURA as a person? He was complex. I found him a pleasant conversationalist, with a broad knowledge of both Eastern and Western culture. His interests were catholic and he had a wide-ranging curiosity. He enjoyed science fiction, particularly ARTHUR CLARKE. He was impressed by the powerful writing of SOPHOCLES, which he picked up as a paperback. He admired BERTRAND RUSSELL. Over the years we had many fruitful discussions, including a number of friendly scientific disagreements (KIMURA 1988). With his close friends he was generous, helpful, and appreciative. But others saw a different side. He could be self-centered, demanding, and dogmatic. As he grew older, his interests narrowed, and he became increasingly concerned for his place in scientific history and more obsessive about his neutral theory. He was becoming recognized throughout the world, and in Japan he was a celebrity. Ironically, these traits increased with his growing scientific recognition. Scientific disagreements became personal and several felt his barbs. But the scars will disappear as people measure them against his sterling accomplishments.

The definitive collection of his papers (KIMURA 1994) happily appeared a few days before his death, and he had a chance to see it. This is the best place to view the

magnitude and variety of his accomplishments. TAKAHATA's introductions are particularly helpful in setting the stage and placing the papers in context.

MOTOO KIMURA is survived by his wife HIROKO and by a son AKIO, his wife MOTOKO and their daughter HANAKO.

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